Section II (Remarks)

Request for One Month Extension of Time

Request is made under the provisions of 37 CFR 1.136 for a one month extension of time. The fee of $65.00 is being paid by on-line credit card payment at the time of EFS filing of this Response to the June 12, 2009 Office Action.

Authorization also is hereby given to charge the amount of any additional fee or amount properly payable in connection with the filing and entry of this Response, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

Addition of New Claims 21 and 22

New claims 21 and 22 have been added herein, directed to specific aspects of the invention.

Claim 21 recites

> **21. A method of preparing nanoparticles incorporating an active ingredient, comprising:**
>
> **dissolving polymers, comprising polylactic co-glycolic acid and a poloxamer, in dichloromethane to form a solution;**
>
> **adding the solution under stirring conditions to a polar phase including ethanol and water, to yield a liquid medium and form the nanoparticles therein; and**
>
> **removing dichloromethane and ethanol from the liquid medium, to concentrate the nanoparticles in aqueous medium;**
>
> **wherein the active ingredient is dissolved in the dichloromethane before or after the polymers are dissolved therein, or the active ingredient is dissolved in an aqueous phase that is dispersed in the dichloromethane before or after the polymers are dissolved therein.**

Such claim is consistent with the disclosure in the application at page 12, line 23 to page 16, line 28 (Examples 1-5), which describe the preparation of nanoparticles in the manner recited in

claim 21. The addition of the active ingredient is recited in terms consistent with those of pending claim 1, reciting the active ingredient as being dissolved in the organic solvent used in the dissolution of the polymers, before or after such polymer dissolution, or dissolved in a small volume of an aqueous phase which is then dispersed in the organic solvent used to dissolve the polymers, before or after such polymer dissolution step.

Claim 22 has been added, of dependent form under claim 21, reciting:

> **22. The method of claim 21, wherein the active ingredient is dissolved in an aqueous phase that is dispersed in the dichloromethane before or after the polymers are dissolved therein.**

Such claim is supported by the disclosure at page 18, lines 5-7 ("[t]he pEGf P-C1 plasmid model (coder of a green fluorescent protein) was incorporated in the internal aqueous phase of the formulations") – i.e., the active ingredient (the DNA encoding green fluorescent protein) was dissolved in an aqueous phase that was dispersed in dichloromethane according to the procedure of Examples 1, 2, 3 and 4.

Accordingly, no new matter (35 USC §132) has been introduced by the newly added claims 21 and 22.

Amendment of Claims 1, 6, 19 and 20

Claim 1 has been amended in this response to specify the polyoxyethylene-derived block copolymer as being "selected from poloxamers and poloxamines," consistent with the disclosure at page 9, lines 9-11 ("[a]ccording to other forms of preferred embodiment, the block copolymer is selected from poloxamers and polyoxamines").

In addition, claim 1 has been amended to provide opening parentheses before the alphabetic characters denoting the respective dissolving, adding, eliminating and isolating steps set forth in the claim.

Further, to accommodate antecedent considerations, the definite article ("the") has been changed to the indefinite article ("an") in the final sub-paragraph of claim 1, and the phrase "wherein the method does not involve a cholesterol compound" in the final phrase of such sub-paragraph has been deleted.

Claim 6 has been amended to recite that the block copolymer "is" a poloxamer. The term "is" thereby replaces the previously recited term "comprises".

Claim 19 has been amended for specificity, recite the method of claim 1, consisting of steps (a) to (d) and the additional step of (i) dissolving an active ingredient in the organic solvent used in (a) before or after step (a), or (ii) dissolving an active ingredient in a small volume of an aqueous phase, which is then dispersed in the organic solvent used in (a), before or after step (a). Such additional step is recited in claim 1, but has been expressly set forth in amended claim 19 to specify the scope of the "consisting" language in such claim.

Claim 20 has been amended to recite "polxamer" in place of "polyoxyethylene-derived polymer," to provide better antecedent basis within such claim 20.

Accordingly, no new matter (35 USC §132) has been introduced by the amendments of claims 1, 6, 19 and 20.

Rejection of Claims Under 35 USC §112, 1st Paragraph

In the June 12, 2009 Office Action, claims 1-20 were rejected (new matter rejection) under 35 USC §112, 1st paragraph, as failing to comply with the written description requirement, based on the recitation in claim 1 that "the method does not involve a cholesterol compound."

Since claim 1 has now been amended to delete this recital ("the method does not involve a cholesterol compound"), such ground of rejection is now moot. It therefore is requested that this 35 USC §112, 1st paragraph new matter rejection be withdrawn.

In the June 12, 2009 Office Action, claims 1-20 were also rejected under 35 USC §112, 1st paragraph, as failing to comply with the written description requirement, on the basis that none of the polyoxyethylene-derived block copolymers other than those explicitly identified in the application, e.g., poloxomers and poloxamines, meet the written description requirement.

In response, claim 1 has been amended to recite that the polyoxyethylene-derived block copolymer is "selected from poloxomers and poloxamines."

Claim 20 has been correspondingly amended for consistency with amended claim 1.

Accordingly, such 35 USC §112, 1st paragraph rejection is overcome, since the Examiner has identified poloxamers and poloxamines as polyoxyethylene-derived block copolymers that meet the written description requirement ("[n]one of the polyoxyethylene-derived block copolymers other than those explicitly identified in the Application (e.g., poloxamers and poloxamines) meet the written description provision of 35 USC §112, 1st paragraph").

It therefore is requested that such 35 USC §112, 1st paragraph written description rejection be withdrawn.

In addition, in the June 12, 2009 Office Action, claims 1-20 have been rejected under 35 USC §112, 1st paragraph, on the basis that the specification, while being enabled for methods of making nanoparticles presented in the specification, lacks enablement for all methods of making nanoparticles encompassed by the instant claims.

This enablement rejection is elaborated pages 4-6 of the June 12, 2009 Office Action. After a recital of the *Wands* factors, it is acknowledged at page 5 of the Office Action that "[t]he relative skill of those skilled in the art is high," but the subsequent discussion at page 6 of the Office Action takes issue with the Declaration evidence submitted on May 6, 2009 (Declaration of Pena and Martinez), from which the conclusion is drawn in the Office Action that:

> **"[u]ndue experimentation would be required to determine which combination(s) of biodegradable polymers and polyoxyethylene-derived block copolymers in what weight ratios within the limits specified by**

> **Applicant do result in the formation of nanoparticles and those combinations of ingredients result which do not, as methods involving the same biodegradable formulation and the PLURONIC® polymer do not all results [sic] in the formation of particles as required by the instant claims."**
>
> (page 6, lines 17-22 of the June 12, 2009 Office Action)

This conclusion of the June 12, 2009 Office Action reflects an erroneous interpretation of the experimental results presented in the Pena/Martinez Declaration. Example A (with cholesterol in the formulation) and Example B (without cholesterol in the formulation) presented in the Declaration reproduce the process disclosed in the previously cited Grandfils reference, a process that is fundamentally different from the method broadly specified by applicants' amended claim 1.

In the process of Grandfils, a biodegradable polymer (PLGA) and a polyoxyethylene-derived block copolymer are dissolved in a non-polar organic solvent, following which the solution is heated and afterwards the organic solvent is removed until a dried blend is obtained.

By contrast, in the process of applicants' invention, as broadly recited in amended claim 1, the solution comprising the non-polar solvent and both polymers (the biodegradable polymer, and the copolymer selected from poloxamers and poloxamines) is added to a polar solvent prior to any solvent removal.

Claim 1 recites, *inter alia*,

> **"(a) dissolving a biodegradable polymer together with a polyoxyethylene-derived block copolymer selected from poloxamers and poloxamines, in a nonpolar organic solvent to form a solution, the weight ratio of the biodiegradable polymer to the polyoxyethylene-derived polymer being between 1:0.1 and 1:3;**
>
> **(b) adding, with stirring, the solution obtained in step (a) to a polar phase, wherein the biodegradable polymer has low solubility, precipitating the polymer and forming the nanoparticles;**
>
> **(c) eliminating the organic solvent"** (emphasis added),

and thus, in applicants' claimed invention, organic solvent is not removed until after the solution that contains the biodegradable polymer, block copolymer and nonpolar organic solvent is added with stirring to the polar phase.

Such removal of solvent after the solution that contains the biodegradable polymer, block copolymer and nonpolar organic solvent is added with stirring to the polar phase is also specified in newly added claim 21, which requires, *inter alia*:

> **"dissolving polymers, comprising polylactic co-glycolic acid and a poloxamer, in dichloromethane to form a solution;**
>
> **adding the solution under stirring conditions to a phase including ethanol and water, to yield a liquid medium and form the nanoparticles therein; and**
>
> **removing dichloromethane and ethanol from the liquid medium, to concentrate the nanoparticles in aqueous medium"**
>
> (emphasis added).

The foregoing shows that the process recited in applicants' claims is fundamentally different from the process of the previously cited Grandfils reference.

Further, the organic solvent used in Examples A and B presented in the Pena/Martinez Declaration to dissolve the dried blend is DMSO (dimethylsulfoxide), which is a polar solvent. Thus, the subsequent addition of a dried blend and DMSO to a polar phase is fundamentally different from applicants' claimed invention, which comprises (claim 1):

> **"(a) dissolving a biodegradable polymer together with a polyoxyethylene-derived block copolymer selected from poloxamers and poloxamines, in a nonpolar organic solvent to form a solution, the weight ratio of the biodiegradable polymer to the polyoxyethylene-derived polymer being between 1:0.1 and 1:3;**
>
> **(b) adding, with stirring, the solution obtained in step (a) to a polar phase, wherein the biodegradable polymer has low solubility, precipitating the polymer and forming the nanoparticles;**
>
> **(c) eliminating the organic solvent;"** (emphasis added).

It therefore is evident that the sequence of steps and the reagents used in Examples A and B in the Pena/Martinez Declaration are different from those of applicants' claimed invention, and that the result obtained for Examples A and B as presented in the Declaration cannot be extrapolated to the method of applicants' claimed invention.

In view of such difference between the specific procedure of Examples A and B presented in the Declaration and the method of the applicants' claimed invention, the conclusion that undue experimentation would be required is not correct.

Although some experimentation may be required in specific implementations of the invention to determine optimal weight ratios providing the best results in respect of formation of nanoparticles, such experimentation is of a routine character, and the Examiner has correctly noted that "[t]he relative skill of those skilled in the art is high" in the field of applicants' claimed invention.

Therefore, any experimentation employed in particular applications of the applicants' claimed invention to determine advantageous relative proportions of polymers and advantageous amounts of solvents in relation to such polymers is not undue.

The law is well settled on this point. The fact that experimentation involved in practicing a claimed invention may be time-consuming, expensive or complex does not render such experimentation undue, if the art typically engages in such experimentation. See ***In re Certain Limited-Charge Cell Culture Microcarriers***, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. *sub nom.*; ***Massachusetts Institute of Technology v. A.B. Fortia***, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also ***In re Wands***, 858 F.2d at 737, 8 USPQ2d at 1404.

It is instructive here to consider cases such as those mentioned above that hold that even significant time, expense and complexity of experimentation do not forfeit an applicant's or patentee's broad scope of claim protection where the experimentation is straightforward and conventional in character, within the skill of the art. Indeed, in ***United States v. Telectronics, Inc.***, 857 F.2d 778, 8 USPQ2d 1217(Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989), the CAFC held that no undue experimentation was involved, even where the time and expense were

approximately $50,000 and 6-12 months, respectively, since the empirical effort involved was of a routine and conventional character.

It therefore is requested that the enablement rejection of claims 1-20 on 35 USC §112, 1st paragraph grounds be withdrawn.

Claim Rejections – 35 USC §112, 2nd Paragraph

In the June 12, 2009 Office Action, claims 1-20 have been rejected under 35 USC §112, 2nd paragraph as indefinite for recitation of "*the active ingredient*" in line 8 of claim 1.

In response, claim 1 has been amended as discussed earlier herein, to replace the definite article "the" with the indefinite article "a" and thereby overcome this rejection.

Also in the June 12, 2009 Office Action, claims 1-20 were rejected under 35 USC §112, 2nd paragraph as indefinite for recitation of a "polar phase" in step (b) and "aqueous phase" in the final sub-paragraph of the claim.

The Office Action stated "[i]t also appears that the solution added in step (b) and referred to as a 'polar phase' is the same phase being referred to in line 9 as the 'aqueous phase'." Such statement reflects several misconstructions of the terminology set forth in claim 1, inasmuch as the terminology of claim 1 is fully clear and definite under the requirements of 35 USC §112, 2nd paragraph.

First, it is pointed out that the "solution" recited in step (b) is not the "polar phase" recited in the same step (b). This is evident from the recitation in step (b) of "adding, with stirring, the solution obtained in step (a) to a polar phase." The solution thus is added to a polar phase. It therefore is apparent that the solution on the one hand, and the polar phase on the other hand, are separate materials. It is clear that a thing cannot be added to itself, and consequently, it is clear that the solution recited in step (b) is not the "polar phase," since each of the solution and the polar phase are added to one another in the method of applicants' claimed invention.

It is equally clear that the "aqueous phase" recited in the final sub-paragraph of the claim is different from either one of "the solution" and "polar phase" components recited in step (b).

This is contextually evident from the recital itself in the last sub-paragraph of claim 1:

> **"wherein an active ingredient is dissolved in the organic solvent used in (a) before or after step (a), or is dissolved in a small volume of an aqueous phase, which is then dispersed in the organic solvent used in (a), before or after step (a)."**

From the foregoing recital, it is clear that the active ingredient can be introduced into the nanoparticles in two alternative ways.

In a first mode, the active ingredient can be dissolved in the organic solvent that is used in step (a) to dissolve the biodegradable polymer and polyoxyethylene-derived block copolymer (poloxamer or poloxamine), before or after step (a) has taken place. Stated another way, the active ingredient can be dissolved in the organic solvent prior to dissolving the biodegradable polymer and block copolymer therein. Alternatively, after the biodegradable polymer and block copolymer are dissolved in the nonpolar organic solvent to form the solution, the active ingredient can be itself dissolved into the solution containing the previously dissolved polymers.

In a second mode, the active ingredient can be dissolved in a small volume of an aqueous phase, and the aqueous phase containing the dissolved active ingredient can be dispersed in the organic solvent used in step (a), before or after step (a). Thus, the active ingredient may be dissolved in the small volume of aqueous phase, with the aqueous phase containing the dissolved active ingredient then being dispersed in the organic solvent, following which the organic solvent is used to dissolve the biodegradable polymer and block copolymer. Alternatively, the active ingredient can be dissolved in a small volume aqueous phase, and after the biodegradable polymer and block copolymer are dissolved in the nonpolar organic solvent, the aqueous phase containing the dissolved active ingredient can then be dispersed in the nonpolar organic solvent containing the previously dissolved polymers.

Accordingly, there is no lack of clarity in the recitals relating to the active ingredient in claim 1, and it is evident that the aqueous phase, the nonpolar organic solvent solution and the polar phase are three different components in the methodology of applicants' claimed invention.

Claims 1-20 therefore fully comply with 35 USC §112, 2nd paragraph in respect of such recitals. Newly added claims 21 and 22 are likewise clear and definite.

Concerning the further discussion in the June 12, 2009 Office Action concerning the recital of the absence of a "cholesterol compound" in claim 1 as previously pending in the application, claim 1 has been amended to delete such limitation, and the rejection of claims therefore is moot on this point.

In the June 12, 2009 Office Action, claim 19 was rejected under 35 USC §112, 2nd paragraph as indefinite in respect of steps associated with step (d) in the claim.

In response, claim 19 has been amended herein to recite the method of claim 1, "consisting of steps (a) to (d) and the additional step of (i) dissolving an active ingredient in the organic solvent used in (a) before or after step (a), or (ii) dissolving an active ingredient in a small volume of an aqueous phase, which is then dispersed in the organic solvent used in (a), before or after step (a)."

It therefore is clear that each of the steps (a) to (d) and the additional active ingredient dissolution step are encompassed by the "consisting of" language in the claim.

It is correspondingly requested that the rejection of claim 19 on such ground be withdrawn.

Claim Rejections – 35 USC §103

In the June 12, 2009 Office Action, claims 1-3, 5-7, 10-18 and 20 were rejected under 35 USC §103(a) as obvious over Koll (U.S. 6,346,274) in view of Soppimath (JCR, 2001, 70, 1-20). The Office Action contends that it would be obvious for one skilled in the art to prepare particles with a composition of the microparticles described by Koll using the solvent evaporation process

described by Soppimath, simply adjusting and optimizing the process parameters to result in particles with a size lower than 1 micron.

The applicants traverse such rejection.

It is pointed out that Koll would not have been taken into account by one of ordinary skill in the art in the first instance, since such reference would dissuade the skilled artisan from using a polyoxyethylene-derived copolymer, such as a poloxamer, in the formulation of nanoparticles. As is apparent from column 9, lines 17-22 and Tables 1 and 2, of such reference, the use of Pluronic (a poloxamer) as an additive facilitates the amount of aggregates also increasing the occurrence of deformed particles, in contrast to other additives such as cyclodextrins ("in the case of microparticles containing PEG or Pluronic F127 … an increased occurrence of deformed microparticles was observed").

Accordingly, one of skill in the art would logically avoid use of polyoxyethylene-derived copolymers, such as poloxamers, in favor of other polymeric reagents.

The secondary reference of Soppimath is a general review describing different techniques such as solvent evaporation applied after oil/water and water/oil/water emulsion formation. However, there is no suggestion or any basis in this document about the specific components, amounts and steps recited in amended claim 1. Soppimath is silent about the dissolution in an organic phase of a biodegradable polymer together with a poloxamer or poloxamine.

Based on these teachings, the combination of Koll and Soppimath provides no derivative basis for the method of applicants' claimed invention or the compositions produced by such claimed methodology of applicants' invention.

It therefore is requested that the rejection of claims 1-3, 5-7, 10-18 and 20 based on Koll et al. in view of Soppimath et al. be withdrawn.

In the June 12, 2009 Office Action, claims 1-20 have been rejected under 35 USC §103(a) as unpatentable over Koll et al. and Soppimath et al. as applied to claims 1-3, 5-7, 10-18 and 20 above, and further in view of Levy et al. International Publication WO 96/20698.

Levy discloses the preparation of nanoparticles wherein poloxamers/poloxamines are used as surface modifying agents that are incorporated in the surface of nanoparticles by physical adsorption after nanoparticles have been formed.

Since Levy uses poloxamer/poloxamine ingredients after the nanoparticles have been formed, to modify the surface of such nanoparticles, Levy provides no basis from which one of skill in the art would dissolve such ingredients with a biodegradable polymer in a nonpolar organic solvent as an initial step toward the formation of nanoparticles. Viewed from such perspective, Levy teaches away from applicants' claimed methodology.

In this respect, it is noted that the method of applicants' claimed invention, requiring, *inter alia*,

> **"(a) dissolving a biodegradable polymer together with a polyoxyethylene-derived block copolymer selected from poloxamers and poloxamines, in a nonpolar organic solvent to form a solution, the weight ratio of the biodiegradable polymer to the polyoxyethylene-derived polymer being between 1:0.1 and 1:3;**
>
> **(b) adding, with stirring, the solution obtained in step (a) to a polar phase, wherein the biodegradable polymer has low solubility, precipitating the polymer and forming the nanoparticles"**
>
> (claim 1 as herein amended),

results in nanoparticles in which the poloxamine or poloxamer is located in the core of the nanoparticle and not on the surface of the nanoparticle, as is the case with the post-nanoparticle formation surface modification taught by Levy.

Accordingly, it is requested that the rejection of claims 1-20 based on Koll et al. and Soppimath et al. further in view of Levy et al. be withdrawn.

The newly added claims 21 and 22 patentably delineate over such references, for corresponding reasons.

In view of the various distinctions of the claims of the present application over the references asserted in the June 12, 2009 Office Action, claims 1-22 as amended/added herein are now in form and condition for allowance.

Fee Payable for Added Claims 21 and 22

With the cancellation herein of claim 18, the addition of new claims 21 and 22 increases the number of total claims by one, and does not increase the number of independent claims beyond the number for which payment previously was made.

Accordingly, an added claims fee of $26 is due. Payment of such added claims fee of $26 is being made by on-line credit card authorization at the time of EFS filing of this response.

Authorization is also given to charge the amount of any additional fee properly payable for this response, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

CONCLUSION

Based on the foregoing, all of Applicants' pending claims 1-22 are patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing, and to responsively issue a Notice of Allowance. If any issues require further resolution, the examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same, in order that this application may be passed to issue at an early date.

Respectfully submitted,

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